Medical Progress

Physiology and Pharmacology of Hypothermia

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Homoiothermic organisms react to hypothermia by shivering and thermogenesis to retain their euthermic state. This reactive homeostatic mechanism recruits a strong sympathetic response, which must be suppressed by anesthesia and adjuvants during induced hypothermia. Below 30° C there is significant neural and organ depression associated with cold narcosis. Cardiac arrhythmias and ventricular fibrillation are grave developments when the core temperature is below 28° C. Proper cardiopulmonary support must be instituted in a patient who has induced or accidental hypothermia at these severely hypothermic levels.

Although clinical hypothermia is used to protect the brain and the heart from ischemic insults during an operation, it induces a complex array of physiologic changes in the body that must be appreciated so that optimal care may be provided to a patient.

Hypothermia induces a complex array of physiologic changes that in turn cause abnormal responses to drug administration. An enormous amount of information has been accumulated in the past three decades on the effects of cold on living organisms, but it is not the purpose of this report to exhaustively review other published articles on this subject. Instead, a brief historical note of medical interest, followed by some selected topics of hypothermic physiology and pharmacology, will be presented. I have intentionally taken a simplistic approach to a complex topic in the hope of providing the reader with some useful information about hypothermic patients.

Background

The analgesic and hemostatic effects of cold have been recognized throughout the ages. Hippocrates used snow and ice to check hemorrhage. "Refrigeration" anesthesia was used during the Renaissance. Baron Larrey, Napoleon's surgeon-general, took advantage of the cold battlefield to carry out surgical repair on hypothermic soldiers without additional central nervous system depressants. Following the introduction of ether in 1846, it was recognized that topically applied ether can produce regional anesthesia by freezing tissues. The use of ethyl chloride as a topical anesthetic soon superseded that of ether and is still being used today.

The concept of total body hypothermia was tested by William Cullen in 1755 when he attempted to cool small animals to a state of suspended animation and in 1766 when John Hunter tried unsuccessfully to revive carp after a period of induced freezing.[1] The application of hypothermia to clinical problems in medicine was pioneered by Smith and Fay,[2] who treated cancer patients by reducing their rectal temperature to 24° to 32° C (75° to 90° F) for up to five days. Regression of malignant growths was observed, especially when the cold was applied locally as with carcinoma of the cervix; but in general there was no permanent reversal of the cancerous process. In 1941 Talbott[3] used prolonged total body hypothermia as a means of administering shock therapy to psychotic patients, but with little success and with two cardiac deaths. McQuiston[4] in 1949 advocated total body cooling during operations in children with cyanotic heart disease, but his rationale for the treatment was to reduce oxygen demand more by counteracting hyperthermia than by inducing true hypothermia. The current clinical application of hypothermia stems chiefly from the laboratory observations of Bigelow and associates,[5-8] who suggested the feasibility of complete circulatory arrest to permit an intracardiac operation in a bloodless field. The reduction of oxygen consumption is proportional to the reduction of cellular temperature. The tolerance of tissue to hy-

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poxia is therefore increased during clinical hypothermia. Although surface-induced hypothermia is only used to a limited extent in surgery today, in a selected group of neonatal cardiac operations, the use of induced regional or total body hypothermia has permeated to a variety of surgical procedures where tissue viability might be improved. For the purpose of communication, clinical hypothermia can be divided into (1) mild hypothermia, 32° to 35° C (90° to 95° F); (2) moderate hypothermia, 26° to 31° C (79° to 88° F); (3) deep hypothermia, 20° to 25° C (68° to 77° F); and (4) profound hypothermia, 14° to 19° C (57° to 66° F).

Physiologic Effects

Humans need to maintain a body temperature close to 37° C regardless of the ambient conditions, in contrast to a hibernating animal that goes into a deep sleep from which it can be aroused with a subsequent rise in temperature. The thermoregulatory mechanisms of the hibernating animals are quite different from those of humans; thus, the physiologic changes of hibernating animals during hypothermia cannot be used as models for clinically induced hypothermia. The disparity of published laboratory results stems from the following: the lack of a standard for normal physiology during hypothermia; the application of different experimental conditions, that is, types and depth of anesthesia, adjuvant drugs, spontaneous versus controlled ventilation, control of acid-base changes, rate of cooling and so forth, and the use of different animal species. Aside from the major differences observed between hibernating versus nonhibernating animals, it can be generalized that smaller animals tolerate cold better than larger animals.

The initial response of a homoiothermic organism to external cold is to generate body heat from shivering and to elicit a strong sympathetic response to resist against lowering of the body temperature. Vasoconstriction is profound; oxygen consumption increases; the respiratory rate accelerates; the heart rate, stroke volume and cardiac output increase, and the blood pressure rises. In the inhumane trials carried out by the Nazis at Dachau, in which prisoners were immersed in water at temperatures of 2° to 12° C, reportedly there was initially violent shivering, succeeded by intense muscle rigidity; consciousness became clouded at a rectal temperature of 31° C, and both muscular rigidity and shivering ceased at rectal temperatures of around 27° C.[9] These initial responses to maintain homeostasis are detrimental to a patient in whom hypothermia is induced. Thus, the appropriate administration of anesthetics and adjuvants is important to suppress these responses, to maintain a stable cardiovascular system and to insure a smooth intraoperative course. "Cold narcosis" supervenes at temperatures below 30° C, so that the requirement for central nervous system depressants is greatly reduced.

Metabolism

Total body metabolism, as reflected by lowering of oxygen consumption, is proportionally reduced with

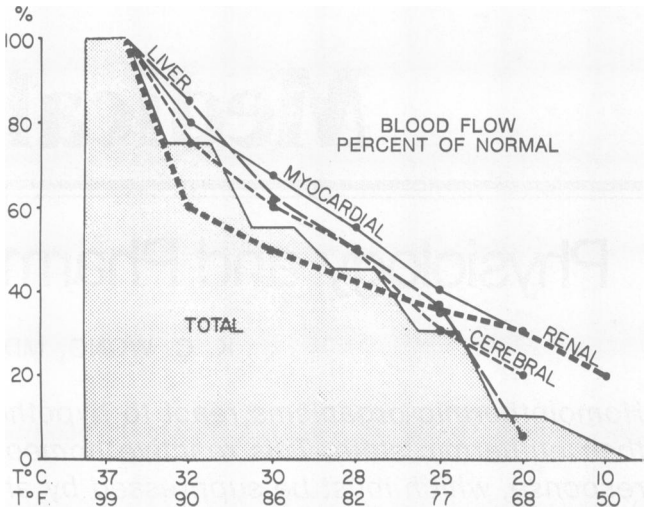

Figure 1.—Blood flow to the organs reduces with progressive hypothermia. The shaded area is total flow. The heart, liver and brain maintain a higher level of flow in comparison with the kidneys to 27° C. However, at 25° to 20° C renal and myocardial blood flows are sustained at 20 percent to 25 percent of normothermic levels whereas cerebral and hepatic blood flow show greater decreases. (Reproduced from Clinical Hypothermia by E. Blair. Copyright [1964, McGraw-Hill]. Used with the permission of McGraw-Hill Book Company.)

progressive hypothermia administered under anesthesia. Whether this fall in oxygen consumption is linearly or exponentially related to the drop in body temperature is still controversial. From a practical viewpoint there is roughly a 6 percent fall in oxygen consumption per degree-Celsius fall in body temperature within the range of hypothermia used clinically today.[10] The earlier estimates suggest that oxygen consumption by dogs is reduced to 50 percent of normal at 30° C[7] and 16 percent of normal at 23° C.[11] More recent data obtained from direct measurements of oxygen consumed by dogs from a closed anesthetic circuit show a 50 percent reduction of oxygen consumption at 28° C and a 75 percent reduction at 20° C.[12,13] These changes obey, in general, van't Hoff-Arrhenius's law, which states that the rate of chemical reaction is doubled for each 10° C rise in temperature or halved for each 10° C fall in temperature. The measurement of total body oxygen consumption to reflect the metabolic state of the body is analogous to the measurement of arterial blood pressure to reflect the circulation. Both are the net result of multiple organ responses.

The extent of the reduction in metabolism of individual organs would not be the same even if all the organs in the core were reduced to the same temperature. At normothermia, oxygen consumption is the highest in the kidney, which consumes 8 percent of total body oxygen while representing only 0.5 percent of the weight of the body.[14] The liver, heart, brain, skeletal muscle and skin follow a descending order of oxygen consumption. However, renal oxygen consumption during hypothermia to 32° C is most rapidly reduced in comparison with the other organs, with a parallel de-

crease in blood flow during the same period of temperature reduction (Figure 1). Thus the body perceives the kidneys as the most dispensable organs for maintaining homeostasis. Indeed the kidneys are also the first organs to be deprived of blood supply during hemorrhage, hypoxia and general anesthesia. Urinary output is an important clinical reflection of organ perfusion.

Carbohydrate, Protein and Fat Metabolism

The metabolism of carbohydrate during hypothermia is reduced. This is reflected by hyperglycemia proportional to the level of cooling.[15-20] Many factors can contribute to the increase in blood glucose. Inadequate protection from the stress of induced hypothermia can promote glycogenolysis and gluconeogenesis from the stimulation of adrenal catecholamines and glucocorticoids. In the presence of adequate anesthesia hypothermia can still cause defective carbohydrate metabolism. Insulin activity is greatly reduced.[15-17] Renal clearance of glucose is compromised.[18] Enzyme hexokinase, which is inhibited by cold, may fail to catalyze hexose transfer across cell membranes, causing a general reduction in liver function.[19] Glycogen stores in the liver are reduced.[20]

There is a dearth of information about protein and fat metabolism. In general plasma proteins are inconsistently affected during induced deep hypothermia in dogs.[21] A depletion of body stores of fat, carbohydrate and protein progressively worsens and is related to the release of cortisol, catecholamines and other stress hormones, especially during accidental hypothermia.[22]

Water and Electrolyte Balance

Changes in extracellular cation concentrations are not of major significance during mild to moderate hypothermia.[23-26] The plasma potassium level in general is reduced without loss of potassium from the body. Under normothermic conditions, general anesthesia and muscle relaxants can also induce hypokalemia in dogs.[27] Patients under general anesthesia show reduced renal excretion of potassium.[24,25] Cellular loss of potassium during deep hypothermia has been implicated in the genesis of cardiac rhythm disturbance[23,28-30] observed at temperatures below 25° C (see the more detailed discussion of cardiovascular metabolism below). Plasma sodium, calcium and chloride concentrations do not change appreciably until the temperature is below 25° C.[23] Hyperkalemia during deep hypothermia is an ominous sign and generally indicates tissue hypoxia.[26]

No significant alterations in body fluids are observed in dogs anesthetized for a short time at 27° to 20°C.[23] However, prolonged cooling at temperatures below 25° C increases cellular water production and decreases plasma volume.[31] It is generally believed that fluid is also sequestered in capillaries during hypothermia; the addition of hemoconcentration and increased blood viscosity to an already compromised circulatory state results in a serious problem for perfusion.[22,32]

Respiration

Hypothermia initially stimulates spontaneous respiration but then ultimately depresses it. Except for the early transient increases observed during the initial cooling period,[6,33] a close relationship exists between the fall in body temperature and the decrease in the respiratory rate and depth.

Cessation of spontaneous respiration is observed at 24° C during experiments with dogs.[33] Respiration must be supported during induced deep hypothermia. But hibernating animals and some accidental hypothermic victims can maintain spontaneous respiration appropriate to the need for carbon dioxide elimination by the lungs. Thus the importance of anesthetic depression of respiratory centers during induced hypothermia has been well recognized.[33-36]

Both physiologic and anatomic respiratory dead spaces are increased during hypothermia. The mechanism is probably cold bronchial dilation.[35] Alveolar dead space is unchanged. The pulmonary exchange of both oxygen and carbon dioxide is not significantly affected during hypothermia.[10] The reduced ventilation is due to a reduction of metabolic requirement and a direct effect of cold on the nervous system. The reduction in oxygen consumption is accompanied by a reduction in carbon dioxide production and direct cooling depresses the entire nervous system including the respiratory centers.[33] Maximal sensitivity of respiratory centers to carbon dioxide stimulation is around 34° C (94° F), whereas the response to hypoxic drive is maintained even at deep hypothermic levels.[37] In animals both carbon dioxide and hypoxic stimulation for respiratory drive are largely gone at 20° C.

Cardiovascular

The effects of hypothermia on the cardiovascular system have been widely studied because the application of clinical hypothermia in modern times has focused on cardiac surgery and myocardial preservation. Again, if the initial sympathetic response to induced hypothermia is suppressed by anesthesia or drugs, there is a proportional decrease in cardiac output, heart rate and mean arterial blood pressure, with little change in stroke volume and an increase in peripheral vascular resistance.[8,11-13,26,32,38] The reduced cardiac output is primarily the result of a slowed heart rate, which slows to about 50 percent of normothermic levels at 28° C and about 20 percent of normothermic levels at 20° C in laboratory animals[12,13,26] and in humans.[32] These percent decreases in heart rate are surprisingly close to the percent reduction in total body oxygen consumption from normothermic levels.[11-13] Although the speed of myocardial contractions—that is, dP/dt or dT/dt (P = pressure, t = time and T = tension)—is decreased during hypothermia, the force of contraction is not depressed; thus there has been confusion about whether myocardial contractility is depressed during hypothermia.

The problem of cardiovascular collapse during hypothermia, then, is generally not a problem of myocardial

contraction, but of myocardial arrhythmias during deep hypothermia. Cardiac arrhythmias increase in severity as the body temperature falls below 28° C. The electrocardiogram shows a prolongation of the PR interval, widening of the QRS complex and a prolongation of the QT interval. Elevation of the ST segment or the appearance of a wave[33] rising steeply from the S wave is pathognomonic of hypothermia and warns of the possible onset of ventricular fibrillation, but it is frequently absent. Arrhythmias are frequent at temperatures below 28° C and may take the form of a nodal rhythm, premature ventricular contractions, atrioventricular block or even ventricular fibrillation.[6,28,32,33,37,38]

The major cause of death of an accidental hypothermic victim or an induced hypothermic patient is ventricular fibrillation, leading to cardiac standstill, the cause of which has been the subject of extensive and innovative studies. Although the mechanism of ventricular fibrillation during hypothermia is still not clearly defined, the following factors have been implicated[28, 39-42]: myocardial hypoxia, electrophysiologic disturbance and autonomic nervous system imbalance. When oxygen supply does not meet the demand of the myocardium, ventricular fibrillation can be the ultimate outcome. This is expected regardless of the temperature of the myocardium. Reduction in coronary blood flow during hypothermia from coronary vasoconstriction[43] and increased viscosity of the blood[32,42] are likely factors contributing to myocardial hypoxia.

Acid-base disturbance occurs with increased frequency during hypothermia below 25° C, unless adequate ventilation is maintained. Extracellular sodium and potassium concentrations are decreased and the chloride level is increased.[29,30] These electrolyte effects are enhanced by acid-base imbalance. That infusion of glucose results in greater myocardial uptake of potassium[29,30] and a lower incidence of ventricular fibrillation suggests a reduction in cellular potassium during hypothermia, which predisposes to ventricular irritability and fibrillation. Myocardial rhythmicity and contractility are significantly influenced by sympathetic and parasympathetic control. Anesthetics have a profound influence on the heart during induced hypothermia. Cyclopropane and pentobarbital are associated with a high incidence of ventricular arrhythmias, whereas ether and thiopental have the lowest incidence of ventricular arrhythmias in experimental animals and in humans.[32,44-49] Reduction of sympathetic activity tends to protect against hypothermic cardiac arrhythmias. That ether maintains a normal sinus rhythm, even at deep hypothermic levels, in dogs and in cardiac surgical infants suggests two important mechanisms for minimizing cardiac arrhythmias during hypothermia[44-49]: the maintenance of the sinoatrial node as the principal pacemaker and the suppression of ventricular irritability and ectopic foci.

Blood

Hypothermia causes a rise in hematocrit and an increase in viscosity with leukopenia and thrombocytopenia.[50,51] A temporary loss of plasma from the circulating volume either as a result of trapping in small peripheral vessels or an actual shift of water to the tissues is a contributing factor.[51,52] Leukopenia and thrombocytopenia are the result of sequestration of these cells in the liver and spleen and possibly also in the intestine and bone marrow. Thus, prolonged bleeding and clotting times are evident at 20° C.[53,54] These changes may not occur at moderate hypothermic levels and are reversible when rewarming from deep to moderate hypothermia.[32,54]

Blood Gas

The use of arterial blood gas determinations as an aid to patient care is an expected standard of medical practice today. Whereas there is general agreement that the arterial pH and partial carbon dioxide pressure (P_{CO_2}) of humans at 37° C should be around 7.40 and 40 mm of mercury, respectively, their ideal values at hypothermic levels are not well established. The problem with trying to establish normality of blood gas values during hypothermia stems from the fact that proper ventilation during hypothermia has not been clearly defined. Over two decades ago, Severinghaus[55] had suggested that "normal ventilation is that in which CO_2 elimination equals its rate of metabolic production as cooling progresses." From a metabolic standpoint, this definition must be correct, but how to interpret the blood gas value at hypothermic levels has posed problems, which have been the subject of recently published articles.[56-59]

A blood gas is generally measured at 37° C, the temperature of the electrodes. It has been customary, then, to correct the values to the patient's body temperature at which the blood was drawn. This generally accepted practice is based on the assumption that the ideal blood gas values at 37° C should be the physiologic standard with which hypothermic levels should be compared. However, a blood gas determined at 37° C with values of partial oxygen pressure (P_{O_2}) 120 and P_{CO_2} 40 mm of mercury and pH 7.4 will have corrected values of 84 and 32 mm of mercury and a pH of 7.48 at 32° C and 59 and 25 mm of mercury and a pH of 7.55 at 27° C by the Severinghaus corrections.[60] The question is whether these values represent hypoxemia and alkalosis during progressive hypothermia.

Rahn and co-workers[59] have suggested that the ideal state for the intermediary metabolism of cells is that of neutrality, because maximal cellular retention of ionized biosynthetic metabolites should occur at pH = pOH (the concentration of hydroxide ions). To defend cellular neutrality and to eliminate acid metabolites and carbon dioxide from the cell, an extracellular alkaline environment is provided by a compliant protein buffer, imidazole of histidine. Thus, at pH 7.4 the blood maintains a ratio of hydroxide ion (OH^-) to hydrogen ion (H^+) of 20:1 and a cellular pH of 6.8 where the OH^- to H^+ ratio is 1:1. This pH gradient between cells and blood of 35 vertebrates was maintained between 0° C to 40° C in vivo, while the bicarbonate content in each species was essentially constant with the

change in temperatures.[61] A constant bicarbonate content gives rise to a constant total blood carbon dioxide content. During hypothermia the reduction in oxygen consumption also results in a reduction in carbon dioxide production; the solubility of carbon dioxide in blood is increased, however. Therefore, alkalosis and hypocarbia during hypothermia are defended by physiologic mechanisms and physical behavior of gases. The use of the uncorrected values of pH and therefore P_{CO_2} in managing a hypothermic patient has thus been advocated.[56-59]

The addition of carbon dioxide during clinical hypothermia and extracorporeal circulation is based on the concern for cerebral perfusion associated with hypocarbia. The concern for cerebral hypoxemia may not be warranted since most laboratory studies have suggested that cerebral metabolism remains aerobic while the reduction in total body oxygen consumption is proportional to the reduction in cardiac output. In fact, maintaining a constant pulmonary ventilation during hypothermia and "respiratory alkalosis" results in better myocardial function in animals[12,13,26,62] and in humans.[32,44] This author also agrees with the clinical practice of not correcting the blood gas values read at 37° C to the temperature of the patient. Acceptable blood gas values measured at 37° C, the temperature of the electrode, require no alteration of mechanical ventilation or inspired carbon dioxide and oxygen concentrations.

Pharmacology

Since it is known that hypothermia depresses organ functions physiologically and biochemically, it is not surprising that all drug responses are exaggerated during hypothermia. Anesthetic requirements for inhalational anesthetics are uniformly decreased during moderate hypothermia.[63] Barbiturate toxicity is not only exaggerated by hypothermia, but hypothermia is reciprocally enhanced by barbiturate depression of thermoregulatory centers of the brain.[64] Phenothiazines by virtue of their α-adrenergic blocking action, in addition to their influence on the thermoregulatory centers, can also potentiate hypothermia.[65] The heart becomes increasingly sensitive to potassium-induced arrest and to calcium-induced fibrillation.[66] The requirement for a cardiotonic dose of digitalis glycosides is generally reduced,[67,68] but the cardiotoxic dose is increased.[69] The myocardium is also more tolerant of the cardiac depressant effects of morphine.[70] In general the cardiac stimulating effects of catecholamines and ketamine are enhanced during mild to moderate hypothermia and depressed at deep hypothermia.[71]

The termination of a drug response is usually the result of metabolism or excretion, or both. Both functions are progressively depressed during hypothermia. It is reasonable, then, to predict that all drugs tend to exert exaggerated responses during progressive hypothermia. The exception is the heart where the contractile process tends to be more resistant to depression during mild to moderate hypothermia.

Accidental Hypothermia

Unintentional exposure to cold from weather[72,73] or to the elements of an operating room is not uncommon. Operating room personnel are well aware of the rapidity by which anesthetized infants or burned patients can lose body heat if appropriate measures are not taken. Despite all precautions, it is at times impossible to maintain normothermia in patients with an open abdomen requiring transfusion of large amounts of fluid and blood. Acidosis and vasoconstriction as a consequence must be judiciously treated to ensure cardiovascular stability during the immediate postoperative period. In general, mild hypothermia can be effectively treated by surface rewarming and heated inspired gases and intravenously given fluids.

When there is moderate to deep hypothermia, particular attention should be given to cardiopulmonary support. Arterial catheterization for continuous pressure monitoring and blood gas determinations is indispensable. A pulmonary arterial catheter may be helpful, especially when cardiac output can be followed by a thermodilution technique. However, the risk of cardiac arrhythmias from introducing the catheter may be significant,[74] especially in an already vulnerable hypothermic heart. Bladder catheterization is important to monitor urinary output, which may also reflect adequacy of intravascular volume and organ perfusion. Of course, the core temperature must be continuously monitored.

Surface rewarming following moderate or deep hypothermia may worsen an already precarious clinical situation. Sequestrated cold fluids may be released from the peripheral vascular beds into the core bloodstream that will prolong the temperature gradient between the core and the periphery. Dilation of the peripheral vascular bed may induce hypotension and cardiac depression from the influx of cold fluid and acid metabolites released from these beds to the heart.[22] A hypothermic heart may not be able to respond to metabolic demands of the warm peripheral tissues. If surface rewarming is instituted for these patients, care must be exercised to not rewarm the patient too quickly, based on arterial blood gas values and cardiovascular stability. Extracorporeal rewarming may be necessary for deeply hypothermic victims.

Consciousness is usually lost at temperatures below 30° C. The use of corticosteroids has been advocated to prevent cerebral edema in an unconscious hypothermic patient.[22,32,73] Erythrocyte agglutination and sludging are associated with increased blood viscosity and deep hypothermia. Dextran 40 is useful for treating such patients during accidental or clinical hypothermia.[22,32] Rarely, an ominous, acute hemorrhagic pancreatitis may develop following prolonged hypothermia with subsequent rewarming.[22]

Finally, it is easy to be too zealous with the treatment of a hypothermic patient. One must always bear in mind when treating such patients that normothermia is not the standard on which to compare. A heart rate of 50 beats a minute with a mean arterial pressure of 60

mm of mercury may be quite adequate for a patient at 27° C.

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